AMENDMENTS TO THE DRAWINGS

Figure 1 has been amended to change each occurrence of "REGFm" to read "EGFRm" and to change "ACF" to read "CFA." A replacement sheet for Figure 1 reflecting these changes is attached.

Figure 5 has been amended to change each occurrence of "REGFm" to read "EGFRm" and to change "ACF" to read "CFA." A replacement sheet for Figure 5 reflecting these changes is attached.

Attachment: Replacement Sheets for Figure 1 and 5.

REMARKS

Drawings

The drawings have been corrected as noted by the Examiner. Namely, Figures 1 and 5 have been amended to change each occurrence of "REGFm" to read "EGFRm" and to change each occurrence of "ACF" to read "CFA." Replacement figures have been provided.

Applicants submit that the above amendments do not add any new matter, and their entry is requested.

Oath

Applicants note that a substitute Declaration is required and are in the process of obtaining the necessary signatures for this declaration. However, because several inventors are located in other countries, obtaining the necessary signatures is requiring more time. A substitute Declaration will be submitted as soon as it is fully executed.

Summary of the Present Invention

The present invention is directed to a pharmaceutical composition that potentiates the immunogenicity of low immunogenic antigens. The composition comprises the low immunogenic antigens and a vaccine carrier. The vaccine carrier consists of very small size proteoliposomes (VSSPs). The VSSPs are derived from the Outer Membrane Protein Complex (OMPC) of *Neisseria meningitidis* and include gangliosides that have been incorporated into the OMPC. The low immunogenic antigens are selected from the group consisting of peptides, polypeptides, proteins and their corresponding nucleic acid sequences. The antigens have not been structurally modified, i.e., they remain in the native form, and have not been incorporated into the VSSPs. The vaccine carrier stimulates and potentiates the immune response against the low immunogenic antigen. Both the humoral immune response and the cellular immune response are stimulated and potentiated by the vaccine carrier. As noted, the immune response is against the low immunogenic antigen which is a

peptide, etc. as set forth in the claims. The potentiation of the cellular immune response includes a potentiation of the induction ability of cytotoxic T cells, such as $CD8^+$ T cells as shown in Example 18.

Rejection Under 35 U.S.C. § 112, first paragraph

The Examiner has rejected claims 1, 3-11 and 27-29 under 35 U.S.C. § 112, first paragraph for lack of written description. The Examiner contends that the language "the antigen is not structurally changed" has no clear support in the specification and claims as originally filed and is thus new matter. Applicants submit that the Examiner is in error in this rejection.

Applicants submit that support for this language can be found at, for example, paragraphs 17 and 21 of the published application. Paragraph 17 describe formulations that confer immunogenicity to "peptides, polypeptides, proteins, and their corresponding DNA sequences" without the need of structural changes in "said antigens." The Examiner contends that there is no antecedent basis for the term "said antigens" in this paragraph. However, the Examiner has failed to read the paragraph in the manner as written. It is clear from this paragraph that "said antigens" are the ""peptides, polypeptides, proteins, and their corresponding DNA sequences," i.e., the substance referred to in the beginning of the paragraph. In addition, a skilled artisan knows that immunogenicity is a property that relates to antigens, and thus increasing the immunogenicity of "peptides, polypeptides, proteins, and their corresponding DNA sequences" is increasing the immunogenicity to these antigens.

In addition to paragraph 17, Applicants note that paragraph 29 of the published application specifies that peptides, polypeptides, proteins and their corresponding nucleic acid sequences are low immunogenic antigens. Thus, it is clear to a skilled artisan that the language "peptides, polypeptides, proteins, and their corresponding DNA sequences" in paragraph 17 and reference to "said antigens" in the same paragraph refer to the same molecules, especially in view of paragraph 29. Also, the claims as originally filed disclosed that peptides, polypeptides, proteins and their corresponding nucleic acid sequences are low immunogenic antigens. Thus, a skilled artisan reading

the application as a whole would understand that peptides, polypeptides, proteins and their corresponding nucleic acid sequences are antigens and that paragraph 17 discloses that they are not structurally changed. Thus, Applicants submit that the specification provides support for the claimed genus of antigens that are not structurally changed.

Furthermore, the objected language is fully supported by the Abstract. The first paragraph of the abstract contains similar language as that found in paragraph 17, except that it is clearer that no structural changes are made in the antigens. Specifically, that abstract states "without making structural changes in said antigens." Similarly, the third paragraph of the abstract states "low immunogenic antigens, such as growth factors, without imparting structural changes therein." These additional passages in the abstract clearly provide further support for the claimed subject matter, especially when the specification is read in its entirety for its disclosure of peptides, polypeptides, proteins and their corresponding nucleic acid sequences as low immunogenic antigens. Thus, Applicants submit that the specification provides support for the claimed genus of antigens that are not structurally changed.

For all of the above reasons, Applicants submit that the specification fully supports the term "the antigen is not structurally changed," and thus it is not new matter. Withdrawal of this rejection is requested.

Rejection Under 35 U.S.C. § 103(a)

The Examiner has rejected claims 1, 6-11 and 27 under 35 U.S.C. § 103(a) as being obvious over Estevez et al. (*Vaccine* **18**:190-197, 2000). The Examiner contends that Estevez et al. teaches that immunization using VSSPs derived from the OMPC of *Neisseria meningitides* with gangliosides hydrophobically incorporated into the OMPC resulted in significant levels of T-dependent igG1, IgG2a and IgG2b (cellular) as well as T-independent IgG3 and IgM (humoral) immune responses in which no immunogenicity was observed when self-gangliosides were used for immunization. The Examiner cites the abstract for the disclosure that VSSPs overcame the natural tolerance to low-immunogenic self-antigen gangliosides in an adjuvant-dependent fashion. The Examiner cites page

196 for the disclosure that it was known that the serotype proteins that are the main components of the OMPC induce proliferation and activation of lymphocytes and lead to the secretion of IL-2. The Examiner also refers to the disclosure in Estevez et al. of the use of Incomplete Fruend's Adjuvant and Montanide ISA 51 the immunization. The Examiner also states that Estevez et al. discloses that mice immunized with VSSPs derived from the OMPC of *Neisseria meningitides* with gangliosides incorporated therein in combination with Montanide ISA 51 resulted in increased immunoglobulin titres compared to mice immunized with VSSPs without Montanide ISA 51. The Examiner further cites Estevez et al. for teaching that patients suffering from metastatic breast cancer have been immunized with GM3/VSSP and NGcGM3/VSSP vaccines in Montanide ISA 51 for therapy.

The Examiner then contends that since the specification does not define a "structurally changed" antigen, the gangliosides taught by Estevez et al. are the same gangliosides expressed in breast cancer patients and are not structurally changed.

The Examiner then states that Estevez et al. does not teach combining the low-immunogenic gangliosides that are not incorporated into the VSSPs with the GM3/VSSP and NGcGM3/VSSP vaccines.

However, the Examiner contends that it would have been *prima facie* obvious for the skilled artisan who would have been motivated to add unincorporated gangliosides to the GM3/VSSP and NGcGM3/VSSP vaccines of Estevez et al. in order to provide more antigen to produce an immune response for breast cancer therapy. The Examiner also contends that a skilled artisan would have a reasonable expectation of success adding free gangliosides to the GM3/VSSP and NGcGM3/VSSP vaccines and stimulating an immune response to them given Estevez et al. successfully demonstrating that VSSPs increase immunogenicity of the low-immunogenic gangliosides. Finally, the Examiner contends that although the gangliosides are not incorporated into the VSSPs, a skilled artisan would have a reasonable expectation of success of eliciting an immune response to free gangliosides in a combined composition with VSSPs in view of the demonstration that VSSPs are demonstrated as responsible for the adjuvant effect of the ganglioside immune response.

Applicants believe the Examiner's comments to Applicants' prior arguments on page 9 of the Office Action are particularly enlightening. The Examiner states that Applicants' prior arguments concerning unexpected result of the adjuvant property of VSSP for EGFR are not applicable because the new rejection "**addresses only the low immunogenic antigen ganglioside**." (emphasis added) The Examiner then again reiterates that the adjuvant effect for VSSPs or GM3/VSSP and NGcGM3/VSSP vaccines in combination with free gangliosides is reasonably expected and not a surprising result.

Applicants submit that the Examiner is in error in this rejection. The claimed subject matter is not directed to a pharmaceutical composition of VSSPs and a low immunogenic ganglioside which is the basis of the Examiner's rejection. Instead, the claimed subject matter is directed to a pharmaceutical composition of VSSPs and a low immunogenic peptide, low immunogenic polypeptide, low immunogenic protein or corresponding nucleic acid sequence. Gangliosides are clearly not peptides, polypeptides, proteins or nucleic acid sequences that encode them. Thus, the claimed composition is not suggested by Estevez et al. nor is there any basis in Estevez et al. to make the claimed composition.

Applicants note that Estevez et al. only teaches that the hydrophobic insertion into the OMPCs outer lipid layers of an amphopathic ganglioside molecule, such as GM3 gangliosides, renders such poorly immunogenic ganglioside sufficiently immunogenic to generate an immune response to the gangliosides which have been incorporated into the OMPCs outer lipid layers. Thus, Applicants submit that Estevez et al. refers simply to the VSSP vehicle for a technical solution **to one particular problem**, rendering GM3 gangliosides immunogenic. As noted, this enhanced immunogenicity of GM3 gangliosides results from the incorporation of the GM3 gangliosides into the OMPC.

Applicants submit that the scope of teachings in Estevez et al. relates to a vaccine to elicit immunogenicity against gangliosides. In contrast, the scope of the present invention is an adjuvant to elicit the immunogenicity of low immunogenic antigens different from gangliosides. Specifically, as set forth in the present claims, the claimed subject matter is a pharmaceutical composition that

potentiates immunogenicity of low immunogenic antigens that, according to the claims, are peptides, polypeptides, proteins and their corresponding nucleic acid sequences. The low immunogenic antigen is not a ganglioside. The composition comprises the specified antigen and a VSSP which comprises OMPC with incorporated ganglioside. In contrast to the ganglioside which is incorporated into the OMPC to make the VSSP, the claimed antigens are not incorporated into the VSSP. Thus, it is clear that the claimed pharmaceutical composition contains a low immunogenic peptide, polypeptide, protein and its corresponding nucleic acid sequence that is not a ganglioside and is not incorporated into the VSSP. Since Applicants are not adding "unincorporated gangliosides" to the VSSP vaccine of Estevez et al., Applicants submit that the Examiner's rejection is clearly in error.

The Examiner also appears to contend that adding free gangliosides to the VSSPs of Estevez et al. would render a composition in which such gangliosides are not incorporated into the VSSPs. However, the Examiner is incorrect in this contention. Applicants submit that it is not possible to prepare a composition in which gangliosides added to VSSPs would not become incorporated into the VSSPs. Nevertheless, Applicants are not preparing such a composition and such a composition is not the subject matter of the claims. The claimed subject matter is a composition that comprises VSSPs and a low immunogenic antigen (i.e., peptides, polypeptides, proteins and corresponding nucleic acids) which is not structurally changed and which is not incorporated into the VSSPs. Such a composition is not shown or suggested by Estevez et al.

Firstly, Applicants note that VSSP is NOT the OMPC alone, but the VSSP is a preparation with particular physicochemical characteristic and which comprises a conjugate between **OMPC and ganglioside**. Estevez et al. teaches many things about VSSP. However Estevez et al. does not teach that mixing VSSPs with a peptide would induce an immune response against said peptide. Estevez et al. measured **the immunogenicity against gangliosides** when they were conjugated to the OMPC to form the VSSPs. Estevez et al. didn't measure the immune response against any peptide or protein conjugated to OMPC, because none were made nor suggested to be made. In other words, Estevez et al. measured the immunogenicity of the VSSP *per se* and found that, when

injecting animals with the VSSP (OMPC + ganglioside), the immune response raised was basically against the ganglioside.

Applicants submit that the present invention is not obvious at all from the results disclosed in Estevez et al. The present invention does not disclose a conjugate between OMPC and peptides (the inventors do not substitute the ganglioside of the VSSPs with a low immunogenic antigen) to claim that this conjugate increases the immunogenicity of said peptides like Estevez did for the ganglioside. Instead, the inventors found that VSSP preparation (OMPC + ganglioside) described by Estevez et al. increases significantly the immune response against proteins, peptides, polypeptides and their corresponding nucleic acids (the claimed low immunogenic antigens) by simply mixing the VSSP (OMPC + ganglioside) with the low immunogenic antigen.

The composition described by Estevez et al. has **two** components (OMPC and ganglioside) which interact to form the VSSPs. In contrast, the composition of the present invention has **three** components – the two components of Estevez et al. which interact to form VSSPs and the claimed low immunogenic antigen, which is not a ganglioside. The present invention claims the adjuvant properties of VSSP. This finding was surprising, and it couldn't be predicted from Estevez et al. because Estevez et al. teaches the structure of the proteoliposome, i.e., VSSP, that is formed by the interaction of the OMPC in combination with the gangliosides. Moreover, without gangliosides, the VSSPs do not exist. However, in the preparation of the present invention the low immunogenic antigen as defined in the claims is simply mixed with the VSSP preparation (OMPC + ganglioside) (preparing VSSP is not simply mixing OMPC with gangliosides, the procedure is much more complex because the ganglioside is anchored to the structure as shown in Estevez et al.). Therefore, the claimed low immunogenic antigen is the accompanist of gangliosides included in the VSSP and what is novel and inventive is the immune response against the claimed low immunogenic antigen.

As described in detail in Applicants' prior response, it is well known in the art that making a peptide immunogenic requires linking this small molecule to a carrier protein mostly by covalent linking or by including the peptide in a liposome vesicle but never by simply mixing the peptide with any other preparation. Thus, Applicants submit that the present invention provides a better

technical solution for potentiating the immunogenicity of the claimed low immunogenic antigens than that of the prior art.

The Examiner has stated that Estevez et al. teaches that VSSP induces humoral and cellular immune response against the low immunogenic antigens. Applicants respectfully disagree because Estevez et al. only provides evidence of this effect for the gangliosides that are incorporated into the OMPC in the preparation of the VSSPs. Estevez et al. does not disclose or suggest anything with respect to the immunogenicity of the claimed low immunogenic antigens, i.e., peptides, polypeptides, proteins and corresponding nucleic acids.

It is very well known by a skilled artisan that the kind of the immune response depends on the presentation of the antigen to the immune system and on the nature of the antigen. The only antigen that is disclosed in Estevez et al. is a ganglioside, and the immunogenicity of this antigen is potentiated by the incorporation in the OMPC. There is no teaching or suggestion in Estevez et al. of any other type of antigen. Furthermore, Applicants submit that Estevez et al. teaches that the antigen must be incorporated into the OMPC. There is no teaching or suggestion in Estevez et al. that a low immunogenic antigen does not need to be incorporated into the OMPC or the resultant VSSP produced by Estevez et al. As disclosed in the present application, the inventors found that they only had to mix the claimed low immunogenic antigens (i.e., peptides, polypeptides, proteins and corresponding nucleic acids) with the VSSP. As disclosed in the present application, the claimed low immunogenic antigen is neither bound by a covalent linkage nor included in the VSSP proteoliposome. There is no suggestion in Estevez et al. as to any potential interaction between the VSSP and the claimed low immunogenic antigens. Consequently, Applicants submit that it could not be predicted as to the kind of immune response that would be induced against the claimed low immunogenic antigen. Moreover, Applicants submit that if the inventors had not measured an immune response against the low immunogenic antigen, it wouldn't have been unexpected to the skilled artisan. Such a result would be explained by the skilled artisan to be due to the fact that the peptide was not connected to the VSSP and therefore was not presented to the immune system in the appropriate context.

Estevez et al. provides evidence of the effect of VSSP on the immune response against **ganglioside** as a result of the ganglioside being incorporated into the OMPC in the preparation of the VSSP. However, Estevez et al. provides no suggestion that VSSPs would have any effect on the immunogenicity of unincorporated low immunogenic antigens (i.e., peptides, polypeptides, proteins and corresponding nucleic acids). That is, there is no evidence in Estevez et al. concerning the claimed low immunogenic antigens, i.e., peptides, polypeptides, proteins and corresponding nucleic acids. The immune response against the third element (i.e., the unincorporated low immunogenic antigen) couldn't be anticipated from results of Estevez et al. because Estevez et al. didn't provide evidence about the interaction of a third element with the VSSP.

In summary,

Estevez et al.	The present invention
teaches about combining OMPC and ganglioside to make VSSP	relates to VSSP + a low immunogenic antigen (i.e., peptides, polypeptides, proteins and corresponding nucleic acids as claimed)
proposed as a solution to increase the immunogenicity against gangliosides	proposes a solution to increase the immunogenicity against these antigens which are not carbohydrate antigens as are the gangliosides

Thus, Applicants submit that there is no teaching or suggestion in Estevez et al. that VSSPs have any adjuvant capability with respect to low immunogenic antigens (as defined in the claims) which are not structurally modified or which are not incorporated into the VSSPs. Consequently, Applicants submit that Estevez et al. does not render the claimed subject matter obvious.

Furthermore, since the present invention does not claim the addition of unincorporated gangliosides to the VSSPs of Estevez et al., Applicants submit that Estevez et al. does not render the claimed subject matter obvious.

In view of the above amendments and remarks, it is submitted that the claimed subject matter is not obvious from the teachings of Estevez et al. Withdrawal of this rejection is requested.

Concluding Remarks

In view of the above amendments and remarks, it is believed that the present claims satisfy the provisions of the patent statutes and are patentable over the cited prior art. Reconsideration of the application and early notice of allowance are requested. The Examiner is invited to telephone the undersigned to expedite the prosecution of the application.

Respectfully submitted,

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